

## Reduction in self-reported nicotine dependence after stabilization in methadone maintenance treatment

Lubomir Okruhlica<sup>1</sup>, Ferdinand Devinsky<sup>2</sup>,  
Danica Klemplova<sup>1</sup>, Jindra Valentova<sup>1</sup>

### *Summary*

ICD-10 criteria have been used for the assessment of opioid dependence and the Fagerstrom Tolerance Questionnaire (FTQ) to assess tobacco smoking. The mean methadone dose was 106 mg (SD=45) in the studied group, after twelve months in the methadone maintenance treatment programme (MMTP). The mean FTQ score was 6.5 (SD+1.8) before entering, 5.6 (SD+2.1) after stabilization in the MMTP ( $p<0.001$ ) and 3 were non-smokers at the time of the second FTQ testing. No smoking cessation programme has been implemented. The findings do show a tendency for nicotine dependence among patients to fall in their period of stabilization in the MMTP.

Key words: nicotine dependence - methadone maintenance  
- methadone dose - methadone plasma concentration - opioid

### **Introduction**

Tobacco dependence is common among users of other drugs, with tobacco smoking prevalence ranging between 85% and 100% in abusers of alcohol, opioids and cocaine [1,2,3]. Among the five categories of primary drugs abused surveyed, heroin users had the highest level of smoking in Stark's study [4]. Tobacco-related diseases are a leading cause of death in patients previously treated for alcohol dependence and/or for other non-nicotine psychoactive substance dependencies [5,6]. Chiat [7] and Schmitz [8] reported

that the administration of methadone results in substantial, dose-related changes in rates of cigarette smoking by methadone-maintained patients. High rates of smoking among methadone maintenance patients were also described by Clemmey<sup>[9]</sup>. However, Frosch et al.<sup>[10]</sup> demonstrated in their study that illicit substance use, as measured through urine toxicology, was found to increase in a stepwise fashion from non-smokers, to chippers, to heavy smokers. Methadone patients who smoke more are significantly more likely to report problems of not feeling “held” by their methadone dose<sup>[11]</sup>.

The use of nicotine in association with opioid use can pose the question whether this is directed towards a search for rewarding effects through pharmacological brain stimulation, or whether it is an attempt at self-medication of withdrawal symptoms. The objective of the study was to find out if, in the context of the Methadone Maintenance Treatment Programme (MMTP), without any rigid general prescription scheme, or firm ceiling for dosage, and where (1) no signs of withdrawal, (2) no craving and (3) no illicit opiate use are the three guiding principles and indicators of proper dose assessment<sup>[12,13]</sup>, there is any change in smoking habits after stabilization of the patients in the programme. The hypothesis was that there would be no increase in nicotine dependence among patients in the MMTP after their stabilization.

## **Patients and Method**

The MMTP in Bratislava (Slovak Republic), from which the study sample was chosen, had an overall retention rate of 84% after 12 months. There was a proportion of 13% of urine samples which tested positive for morphine. These outcome indicators were presented in The Report on Methadone Maintenance Treatment, which was submitted by The Centre for Treatment of Drug Dependencies to The Slovak Ministry of Health in 2001. Apart from a diagnosis of opioid dependence, additional inclusion criteria were required for admission to the MMTP: age 18 years and over, and at least two documented unsuccessful attempts at medical detoxification with no sustained abstinence. The programme, which was complex, consisted of medical and psychiatric services, group therapy, a cognitive-behavioural approach and contingency management. Methadonium chloratum was dispensed in liquid form mixed with juice at the methadone outpatient clinic. Take-homes were allowed for weekends. At a later stage, patients were allowed to collect methadone twice a week, with the preconditions that they had not had any positive urine tested for morphine in the past twelve months and the daily dose should not exceed 200 mg.

The studied group consisted of 138 subjects who were admitted to the MMTP in Bratislava. The second FTQ testing was conducted during regular status examination after one year of treatment. There were 76% males and 24% of females in this group. The average age was 27.3 years (SD+5.0) in a range between 19 and 44 at the time of their entry to the programme. There were 137 (99%) tobacco smokers and 1 (1%) non-smoker in the group at the time of intake to the programme.

The study had a prospective, clinical design. ICD-10<sup>[14]</sup> diagnostic criteria were used

to assess the diagnosis of opioid dependence. The Fagerstrom Tolerance Questionnaire (FTQ), in its 8-item version [15], was used to measure nicotine dependence. The FTQ was administered for the first time during the pre-entry interview at the time of intake into the MMTP and after one year of treatment. The survey was conducted from June 2001 to June 2002. The correlation between the FTQ score and daily methadone dose was studied in the whole group, and correlation with the methadone concentration in plasma was studied in the subgroup of 64 patients from the sample. Their blood was taken for plasma level assessment after 12 months of being in the programme and the FTQ was administered simultaneously. Quantitative analysis of blood samples for methadone was performed in an analytical laboratory, where the GC/MS methodology was used. Using SPSS statistical software, the following methods were applied: t-test for two independent samples, t-test for matched pairs, one-way ANOVA, Kolmogorov-Smirnov test for goodness of fit, Pearson correlation coefficient.

## Results

The average dose of methadone was 106 mg (SD=45; median 100 mg, in the range between 10 and 230 mg). The frequency distribution curve for doses in the studied group was approximately bell-shaped (Fig. 1). It was tested by a Kolmogorov-Smirnov test. The mean daily dose of methadone in the subgroup of 64 patients, where methadone plasma concentrations were assessed, too, was 107 mg (SD=40; median 100 mg, in the range between 30 and 190 mg).

There were 3 non-smokers at the time of the second FTQ testing: 1 (0.7%) preserved

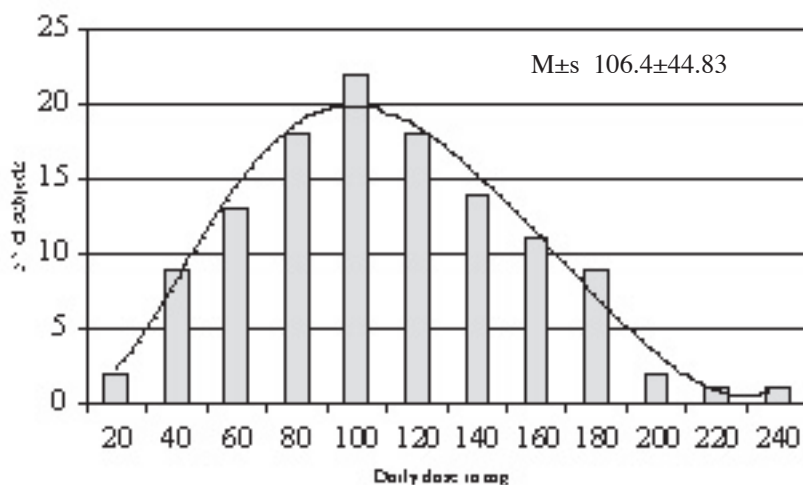


Figure 1. Frequency distribution of daily methadone doses in the group

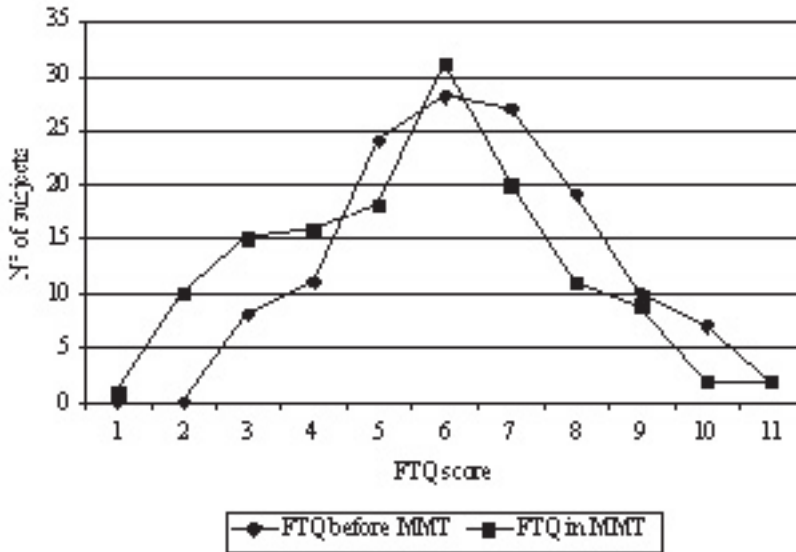


Figure 2. Frequency distributions of FTQ scores in the group before entering MMTP and after stabilization in it

his non-smoking status, which he had prior to the MMTP and 2 (1.4%) gave up smoking while they were in the programme. The mean FTQ score for nicotine dependence was 6.5 (SD=1.8) prior to entering methadone maintenance vs. 5.6 (SD=2.1) at the time of stabilization. The difference between these two mean scores was statistically significant ( $p < 0.001$ ; 95% CI 0.6-1.2). Graphic illustration is provided by two line-charts of score distributions (Fig. 2). No statistically significant differences were confirmed between genders in relation to dosages and FTQ scores. Test-retest reliability of the FTQ was measured (Pearson  $r = 0.535$ ;  $p < 0.01$ ).

No significant correlation was found between the daily methadone dose and the FTQ score, or in the whole studied group (Pearson  $r = 0.090$ ; NS). In the subgroup where plasma concentrations were measured, the correlation between admission FTQ and the dose after one year of treatment was significant at the 0.05 level (Pearson  $r = 0.252$ ;  $p = 0.047$ ); but the correlation disappeared after a year (Pearson  $r = 0.159$ ; NS). No correlation was found between the level of methadone in the plasma and the FTQ score in this subgroup (Pearson  $r = -0.033$ ; NS).

## Discussion

The frequency distribution curve for daily methadone doses was approximately bell-shaped in the studied group. Still, there was a tendency towards a slight shift to the right. This was probably due to the fact that daily doses of methadone above 200 mg were not allowed by the programme for the twice-a-week take-homes; this restriction

was indirectly pushing some of the patients to reduce their daily dose demands below this limit.

We detected a very high proportion (99%) of tobacco smokers among patients with opioid dependence in this sample at the time of their entry to the MMTP. Despite the fact that nicotine has been and continues to be the most common substance abused by patients with opioid dependence, very little is known about optimum treatments for the reduction and cessation of tobacco use in these dual diagnosis patients. There are, however, studies that indicate the feasibility of treating cigarette smoking in the context of drug dependence therapy, especially within the framework of opioid dependence treatment <sup>[6,9, 16]</sup>.

According to Nestler <sup>[17]</sup>, endogenous opioid pathways have been implicated in the acute reinforcing effects, not only of opiates, but also of other abused drugs, particularly alcohol and nicotine. Preliminary pharmacological evidence suggests that there is an opioid component in nicotine dependence. Nicotine-dependent subjects showed naloxone dose-dependent increases in withdrawal signs and craving <sup>[18]</sup>. On the other hand naltrexone was found to significantly reduce craving and the total number of cigarettes smoked in nicotine-dependent subjects <sup>[19]</sup>.

The psychometric characteristics of the Fagerstrom Tolerance Questionnaire and its versions, as an instrument for measuring nicotine dependence, have been discussed in several studies resulting in the conclusion that it is useful <sup>[14, 20, 3, 21]</sup>. Our principal hypothesis, based on our clinical impressions, has been confirmed by the findings of this study, which detected not only that there was no increase in nicotine dependence, but that there was actually a decrease in the mean FTQ score among patients after their stabilization in the MMTP (from 6.5 to 5.6). It is interesting that the FTQ score was found to be much higher among patients on methadone maintenance in the work of other authors, e.g. 7.5 in Clemmey's <sup>[9]</sup> study. High rates of smoking among methadone patients, which have been attributed to their desire to intensify the effect of opiates <sup>[1]</sup>, seem to have been a less prevalent cause in this group. Despite finding an increase in smoking after an increase in methadone doses, Stark & Campbell <sup>[22]</sup> found that maintenance doses were not correlated with smoking levels. This might suggest that the acute effects of methadone on smoking are nullified as clients get used to the dose level. This is also consistent with our results. What is important to mention is that no correlation between the methadone dose and the FTQ score (intensity of dependence) was found, but also no correlation could be demonstrated between the FTQ and the concentration of methadone in plasma. This is interesting in association with the unclear influence of smoking on methadone plasma levels. Prevailing opinion, according to Eap <sup>[23]</sup>, was that smoke increases methadone plasma clearance and so induces its faster elimination from the body. However, in an *in vitro* study, human liver microzomes, CYP1A2, did not seem to be involved in the methadone metabolism.

Stabilization on individually tailored doses of methadone, which was associated with a large decrease in the occurrence of opioid withdrawal signs, and in craving, and with a decrease in the use of illicit opiates, could be the basis for this significant change in

smoking habits among the methadone patients in our group. The approach which excludes upper methadone dose limits exists can provide that opportunity. The hypothesis can be put forward that if there is a higher proportion of patients in any MMTP who are on lower methadone maintenance doses and are simultaneously taking illicit opiates, that they are not fully stabilized, so the cigarettes are used as self-medication for the signs of discomfort. This would be consistent with Frosch's [10] findings.

It seems that high rates of cigarette smoking are not an inevitable future for patients in MMTPs. On the basis of these findings, it might be presumed that comprehensive methadone maintenance treatment programmes themselves, with appropriate, individually assessed dosing, could be associated with a reduction in the intensity of nicotine dependence and might be a good starting point for the application of targeted tobacco cessation programmes among patients treated for opioid dependence.

These findings would need further replications in different MMTPs. Also, other objective methods for the assessment of tobacco smoking, such as the measurement of carbon monoxide levels in used air and that of plasma cotinine levels should be applied in studies with a similar design in the future.

## **Conclusions**

Based on the results of this study, it seems that a high level of tobacco dependence is not an inevitable future for patients in MMTPs. We presume that methadone maintenance treatment itself, with appropriate, individually assessed dosing can contribute to the reduction of nicotine dependence and that is a precondition for further effective tobacco cessation efforts among patients treated for opioid dependence.

## **Acknowledgments**

This study was supported by the Protidrogovy Fund in Slovakia and also by the Ministry of Education of Slovak Republic grant No. VEGA 1/7277/20.

## **References**

1. Benowitz NL. (1999). Nicotine addiction. *Primary Care* 26:611-631.
2. Chiat LD, Griffiths RR. (1984). Effects of methadone on human cigarette smoking and subjective ratings. *Journal of Pharmacology and Experimental Therapeutics* 1929:636-640.
3. Clemmey P, Brooner R, Chutuape MA, Kidorf M, Stitzer M. (1997). Smoking habits and attitudes in a Methadone maintenance treatment population. *Drug and Alcohol Dependence* 44:123-132.
4. Eap CB, Déglon, JJ, Baumann P. (1999). Pharmacokinetics and Pharmacogenetics of Methadone: Clinical Relevance. *Heroin Addiction and Related Clinical Problems* 1:19-34.

5. Fagerstrom KO, Schneider NG. (1989). Measuring nicotine dependence: Review of the Fagerstrom Tolerance Questionnaire. *Journal of Behavioral Medicine* 12: 159-182.
6. Finnegan L. (2000). Women, Pregnancy and Methadone. *Heroin Addiction and Related Clinical Problems* 2:1-8.
7. Frosch DL, Shoptaw S, Nahom D, Jarvik ME. (2000). Associations between tobacco smoking and illicit drug use among methadone-maintained opiate dependent individuals. *Experimental and Clinical Psychopharmacology* 8:97-103.
8. Haddock CK, Lando H, Klesges RC, Talcott W, Renaud EA. (1999). A Study of the Psychometric and Predictive Properties of the Fagerstrom Test for Nicotine Dependence in a Population of Young Smokers. *Nicotine & Tobacco Research* 1:116-20.
9. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of Tolerance Questionnaire. *British Journal of Addiction* 86:1119-1127.
10. Hser Y, McCarthy WJ, Anglin MD. (1994). Tobacco use as a distal predictor of mortality among long-term narcotics addicts. *Preventive Medicine* 23:61-69.
11. Hurth RD, Offord KP, Croghan IT, Gomez-Dahl L, Kottke TE, Morse LM, Melton LJ. (1996). Mortality following inpatient addictions treatment: role of tobacco use in a community-based cohort. *JAMA : the Journal of the American Medical Association* 275:1097-1103.
12. King AC, Meyer PJ. (2000). Naltrexone alteration of acute smoking response in nicotine-dependent subjects. *Pharmacology, Biochemistry and Behavior*. 66: 563-572.
13. Kreek MJ. (1999). Rationale for maintenance pharmacotherapy of opiate dependence. In: O'Brein CP, Jaffe JH, eds. *Addictive states. Research publications: Association for Research in Nervous and Mental Disease*. New York: Raven Press.
14. Krishnan-Sarin S, Rosen MI, O'Malley SS. (1999). Naloxone challenge in smokers. Preliminary evidence of an opioid component in nicotine dependence. *Archives of General Psychiatry* 56:663-668.
15. Navaratnam V, Foong K. (1990). Adjunctive drug use among opiate addicts. *Current Medical Research and Opinion* 11:611-619.
16. Nestler EJ. (1998). Neuroadaptation in addiction. In: *Principles of addiction medicine*. Chevy Chase, Maryland: ASAM, pp. 57-71.
17. Richter KP, Ahluwalia JS. (2000). A case of addressing cigarette use in methadone and other opioid treatment programs. *Journal of Addictive Diseases* 19:35-52.
18. Schmitz JM, Grabowski J, Rhoades H. (1994). The effects of high and low doses of methadone on cigarette smoking. *Drug and Alcohol Dependence* 34:237-242.
19. Schmitz JM, Schneider NG, Jarvik ME (1997). Nicotine In: Lowinson HJ, Ruiz P, Millman RB, Langrod JG, eds. *Substance Abuse A Comprehensive Textbook Third Edition*. Baltimore, MA: Williams & Wilkins, pp. 276-294.

20. Stark MJ, Campbell BK. (1993). Cigarette smoking and methadone dose levels. *American Journal of Drug and Alcohol Abuse* 19:209-217.
21. Stark MJ, Campbell BK. (1993). Drug use and cigarette smoking in applicants for drug abuse treatment. *Journal of Substance Abuse* 5:175-185.
22. Tucke U, Wolff K, Finch E, Strang J. (2001). The effect of tobacco smoking on subjective symptoms of inadequacy (“not holding”) of methadone dose among opiate addicts in methadone maintenance treatment. *Addiction Biology* 6:137-145.
23. World Health Organization. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders*. Geneva: World Health Organization.

*Received January 20, 2003 - Accepted March 30, 2003*